REMARKS

1. Support for the amendments and new claim

The current amendments to the claims simply clarify claim language, and thus the amendments do not constitute new matter.

2. Rejection under 35 USC 112, second paragraph

The Patent Office rejected claims 30, 44, and 61-66 under 35 USC 112, second paragraph, based on the assertion that the specification did not provide an adequate written description of the claimed invention. Specifically, the Patent Office asserted that the use of terms "first", "second", and "third" translocation quotients was not supported in the specification as filed and constituted new matter. The Applicants traverse this rejection.

As noted in MPEP 2163.02, the written description requirement of 35 USC 112 requires that a patent specification "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter," citing *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)). "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

As explicitly noted in MPEP 2163.02, "The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." As noted in MPEP 2163.07, "Mere rephrasing of a passage does not constitute new matter. Accordingly, a rewording of a passage where the same meaning remains intact is permissible," citing *In re Anderson*, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973).

The patent office acknowledged that the specification provided written support for "the general act of forming a translocation quotient and comparing values from control and experimental wells..." (See page 3, lines 9-11 of the office action). The patent office objected to the inclusion of terms "first", "second", and "third" translation quotients, asserting that they

were not present in the application as filed, and specifically stated that the cited support for the amended claims "do not specify the particular quotients in the amended phrases listed or a comparison between a control and a control, as the comparison of a first and third translocation quotient in the amended phrase seems to suggest."

The qualifiers "first," "second," and "third" for "translocation quotient" were simply used as a convenience to refer back to the specific control or experimental translocation quotient recited in the claim. The "first" translocation quotient is an experimental value being analyzed (step (e)) and compared to either further experimental values (ie: "second translocation quotients"), which relates to kinetic experiments; and/or compared to controls (ie: the "third" translocation quotient, determined from cells not contacted with the test stimulus. In other words, these qualifiers simply were used to rename the control and experimental quotients which the patent office acknowledged enjoyed adequate written description in the specification. As noted above, "The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement;" also, "Mere rephrasing of a passage does not constitute new matter. Accordingly, a rewording of a passage where the same meaning remains intact is permissible," citing *In re Anderson*, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973). Since the use of "first," "second," and "third," was a mere renaming of terms that are acknowledged by the Patent Office to enjoy support in the specification, the specification does provide adequate written description for the claims as previously pending.

However, solely in order to expedite allowance of the claims, the Applicants have amended the claims to cancel the use of the qualifiers "first," "second," and "third." Since the office action indicates that this is the only written description issue, the Applicants believe that this amendment obviates the written description rejection. The Applicants further note that these amendments in no way serve to limit the scope of the claim.

While the Applicants believe that the above is adequate to overcome the rejection, specific support for the steps (e), (f)(i), and (f)(ii) are, for example, as follows:

(a) Page 69 lines 4-18; and Page 69 lines 19 to page 71 line 3 (for example) provide support for determining a translocation quotient between the cell cytoplasm and the plasma membrane for the cellular macromolecule of interest by calculating a ratio of the intensity of the fluorescent signals from the fluorescent reporter molecules that report on the

one or more cellular macromolecule of interest within the plasma membrane mask and the intensity of the fluorescent signals from the fluorescent reporter molecules that report on the one or more cellular macromolecule of interest within the cell cytoplasm mask in the individual cells in response to contacting the cells at a first time point with a test stimulus (**ie: step (e) of claim 30**)

Page 69 lines 4-18

Rho-RhoGDI complex translocation to the membrane. In another embodiment, indicator cells are ***treated with test compounds*** and then fixed, washed, and permeabilized. The indicator cell plasma membrane, cytoplasm, and nucleus are all labeled with distinctly colored markers followed by immunolocalization of Rho protein (Self et al. (1995), *Methods in Enzymology* 256:3-10; Tanaka et al. (1995), *Methods in Enzymology* 256:41-49) with antibodies labeled with a fourth color. Each of the four labels is imaged separately using the cell screening system, and the images used to ***calculate the amount of inhibition or activation of translocation effected by the test compound***. To do this calculation, the ***images of the probes used to mark the plasma membrane and cytoplasm are used to mask the image of the immunological probe marking the location of intracellular Rho protein***. The integrated brightness per unit area under each mask is used to form a ***translocation quotient by dividing the plasma membrane integrated brightness/area by the cytoplasmic integrated brightness/area***. By ***comparing the translocation quotient values from control and experimental wells***, the percent translocation is calculated for each potential lead compound.

Page 69 lines 19 to page 71 line 3

β-Arrestin translocation to the plasma membrane upon G-protein receptor activation.

In another ***embodiment of a cytoplasm to membrane translocation*** high-content screen, the ***translocation of β-arrestin protein from the cytoplasm to the plasma membrane is measured in response to cell treatment***. To measure the translocation, living indicator cells containing luminescent domain markers are ***treated with test compounds*** and the movement of the β-arrestin marker is measured in time and space using the cell screening system of the present invention. In a preferred embodiment, the indicator cells contain luminescent markers consisting of a green fluorescent protein β-arrestin (GFP-β-arrestin) protein chimera (Barak et al. (1997), *J. Biol. Chem.* 272:27497-27500; Daaka et al. (1998), *J. Biol. Chem.* 273:685-688) that is expressed by the indicator cells through the use of transient or stable cell transfection and other reporters used to mark cytoplasmic and membrane domains. When the indicator

cells are in the resting state, the domain marker molecules partition predominately in the plasma membrane or in the cytoplasm. In the high-content screen, these markers are used to delineate the cell cytoplasm and plasma membrane in distinct channels of fluorescence. ***When the indicator cells are treated with a test compound, the dynamic redistribution of the GFP-β-arrestin is recorded as a series of images over a time scale ranging from 0.1 s to 10 h. In a preferred embodiment, the time scale is 1 h. Each image is analyzed by a method that quantifies the movement of the GFP-β-arrestin protein chimera between the plasma membrane and the cytoplasm. To do this calculation, the images of the probes used to mark the plasma membrane and cytoplasm are used to mask the image of the GFP-β-arrestin probe marking the location of intracellular GFP-β-arrestin protein. The integrated brightness per unit area under each mask is used to form a translocation quotient by dividing the plasma membrane integrated brightness/area by the cytoplasmic integrated brightness/area. By comparing the translocation quotient values from control and experimental wells, the percent translocation is calculated for each potential lead compound. The output of the high-content screen relates quantitative data describing the magnitude of the translocation within a large number of individual cells that have been treated with test compounds of interest.***

(b) **Page 42 lines 1-12; Page 42 line 13 to page 43 line 13; and Page 69 line 19 to page 71 line 3**, provide support for: comparing the translocation quotient determined in step (e) to: i) one or more translocation quotients for the cellular macromolecule of interest between the cell cytoplasm and the plasma membrane, which are determined by calculating a ratio of an intensity of fluorescent signals from the fluorescent reporter molecules that report on the one or more cellular macromolecule of interest within the plasma membrane mask and an intensity of fluorescent signals from the fluorescent reporter molecules that report on the one or more cellular macromolecule of interest within the cell cytoplasm mask in the individual cells in response to contacting the cells with the test stimulus from at least a second time point **(ie: step f(i) of Claim 30)**

Page 42 lines 1-12 (Generic disclosure of kinetic screening applicable to all embodiments, as exemplified on page 69 line to page 71 line 3)**:**

"The kinetic live cell extension of the invention enables the design and use of screens in which a biological process is characterized by its kinetics instead of, or in addition to, its spatial characteristics. In many cases, a

response in live cells can be measured by adding a reagent to a specific well and ***making multiple measurements on that well with the appropriate timing***. This dynamic live cell embodiment of the invention therefore includes apparatus for fluid delivery to individual wells of the system in order to deliver reagents to each well at a specific time in advance of reading the well. ***This embodiment thereby allows kinetic measurements to be made with temporal resolution of seconds to minutes on each well of the plate.*** To improve the overall efficiency of the dynamic live cell system, the acquisition control program is modified to ***allow repetitive data collection from sub-regions of the plate, allowing the system to read other wells between the time points required for an individual well.***

Page 42 line 13 to page 43 line 13 (Generic disclosure of kinetic screening applicable to all embodiments, as exemplified on page 69 line to page 71 line 3)**:**

Figure 8 describes an example of a fluid delivery device for use with the live cell embodiment of the invention and is described above. This set-up allows one set of pipette tips 705, or even a single pipette tip, to deliver reagent to all the wells on the plate. The bank of syringe pumps 701 can be used to deliver fluid to 12 wells simultaneously, or to fewer wells by removing some of the tips 705. The temporal resolution of the system can therefore be adjusted, without sacrificing data collection efficiency, by changing the number of tips and the scan pattern as follows. ***Typically, the data collection and analysis from a single well takes about 5 seconds. Moving from well to well and focusing in a well requires about 5 seconds, so the overall cycle time for a well is about 10 seconds. Therefore, if a single pipette tip is used to deliver fluid to a single well, and data is collected repetitively from that well, measurements can be made with about 5 seconds temporal resolution. If 6 pipette tips are used to deliver fluids to 6 wells simultaneously, and the system repetitively scans all 6 wells, each scan will require 60 seconds, thereby establishing the temporal resolution. For slower processes which only require data collection every 8 minutes, fluids can be delivered to one half of the plate, by moving the plate during the fluid delivery phase, and then repetitively scanning that half of the plate. Therefore, by adjusting the size of the sub-region being scanned on the plate, the temporal resolution can be adjusted without having to insert wait times between acquisitions. Because the system is continuously scanning and acquiring data, the overall time to collect a kinetic data set from the plate is then simply the time to perform a single scan of the plate, multiplied by the number of time points required. Typically, 1 time point before addition of compounds and 2 or 3 time points following addition should be sufficient for screening purposes***.

Page 69 line 19 to page 71 line 3

β-Arrestin translocation to the plasma membrane upon G-protein receptor activation.

In another ***embodiment of a cytoplasm to membrane translocation*** high-content screen, the ***translocation of β-arrestin protein from the cytoplasm to the plasma membrane is measured in response to cell treatment***. To measure the translocation, living indicator cells containing luminescent domain markers are ***treated with test compounds*** and the movement of the β-arrestin marker is measured in time and space using the cell screening system of the present invention. In a preferred embodiment, the indicator cells contain luminescent markers consisting of a green fluorescent protein β-arrestin (GFP-β-arrestin) protein chimera (Barak et al. (1997), *J. Biol. Chem.* 272:27497-27500; Daaka et al. (1998), *J. Biol. Chem.* 273:685-688) that is expressed by the indicator cells through the use of transient or stable cell transfection and other reporters used to mark cytoplasmic and membrane domains. When the indicator cells are in the resting state, the domain marker molecules partition predominately in the plasma membrane or in the cytoplasm. In the high-content screen, these markers are used to delineate the cell cytoplasm and plasma membrane in distinct channels of fluorescence. ***When the indicator cells are treated with a test compound, the dynamic redistribution of the GFP-β-arrestin is recorded as a series of images over a time scale ranging from 0.1 s to 10 h. In a preferred embodiment, the time scale is 1 h. Each image is analyzed by a method that quantifies the movement of the GFP-β-arrestin protein chimera between the plasma membrane and the cytoplasm. To do this calculation, the images of the probes used to mark the plasma membrane and cytoplasm are used to mask the image of the GFP-β-arrestin probe marking the location of intracellular GFP-β-arrestin protein. The integrated brightness per unit area under each mask is used to form a translocation quotient by dividing the plasma membrane integrated brightness/area by the cytoplasmic integrated brightness/area. By comparing the translocation quotient values from control and experimental wells, the percent translocation is calculated for each potential lead compound. The output of the high-content screen relates quantitative data describing the magnitude of the translocation within a large number of individual cells that have been treated with test compounds of interest.***

(c) **Page 69 line 19 to page 71 line 3**, for example, provide support for: comparing the translocation quotient determined in step (e) to: ii)one or more translocation quotients for the cellular macromolecule of interest between the cell cytoplasm and the plasma membrane, which are determined by calculating a ratio of an intensity of fluorescent signals from the fluorescent reporter molecules that report on the one or more cellular macromolecule of

interest within the plasma membrane mask and an intensity of fluorescent signals from the fluorescent reporter molecules that report on the one or more cellular macromolecule of interest within the cell cytoplasm mask in the individual cells that have not been contacted with the test stimulus **(ie: step f(ii) of Claim 30).**

Page 69 line 19 to page 71 line 3

β-Arrestin translocation to the plasma membrane upon G-protein receptor activation.

In another ***embodiment of a cytoplasm to membrane translocation*** high-content screen, the ***translocation of β-arrestin protein from the cytoplasm to the plasma membrane is measured in response to cell treatment***. To measure the translocation, living indicator cells containing luminescent domain markers are ***treated with test compounds*** and the movement of the β-arrestin marker is measured in time and space using the cell screening system of the present invention. In a preferred embodiment, the indicator cells contain luminescent markers consisting of a green fluorescent protein β-arrestin (GFP-β-arrestin) protein chimera (Barak et al. (1997), *J. Biol. Chem.* 272:27497-27500; Daaka et al. (1998), *J. Biol. Chem.* 273:685-688) that is expressed by the indicator cells through the use of transient or stable cell transfection and other reporters used to mark cytoplasmic and membrane domains. ***When the indicator cells are in the resting state, the domain marker molecules partition predominately in the plasma membrane or in the cytoplasm***. In the high-content screen, these markers are used to delineate the cell cytoplasm and plasma membrane in distinct channels of fluorescence. When the indicator cells are treated with a test compound, the dynamic redistribution of the GFP-β-arrestin is recorded as a series of images over a time scale ranging from 0.1 s to 10 h. In a preferred embodiment, the time scale is 1 h. Each image is analyzed by a method that quantifies the movement of the GFP-β-arrestin protein chimera between the plasma membrane and the cytoplasm. To do this calculation, the images of the probes used to mark the plasma membrane and cytoplasm are used to mask the image of the GFP-β-arrestin probe marking the location of intracellular GFP-β-arrestin protein. The integrated brightness per unit area under each mask is used to form a translocation quotient by dividing the plasma membrane integrated brightness/area by the cytoplasmic integrated brightness/area. ***By comparing the translocation quotient values from control and experimental wells, the percent translocation is calculated for each potential lead compound.*** The output of the high-content screen relates quantitative data describing the magnitude of the translocation within a large number of individual cells that have been treated with test compounds of interest.

Based on all of the above, it is clear that the specification as filed provides adequate written support for the claimed invention. Thus, the Applicants respectfully request reconsideration and withdrawal of this rejection.

Based on the foregoing, the Applicants believe that the application is ready for allowance. If the Examiner believes that a telephone or personal interview would expedite prosecution of the instant application, the Patent Office is invited to call the undersigned attorney at (312) 913-2106.

Respectfully Submitted,

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By: _____

David Harper
Reg. No. 42,636
McDonnell, Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, IL 60606